Insights Into Patients' Experience With Type 1 Diabetes: Exit Interviews From Phase III Studies of Sotagliflozin

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ABSTRACT

Purpose: The purpose of this study was to conduct qualitative participant interviews to provide context to the meaningfulness of improvements in end points seen in 2 large-scale Phase III sotagliflozin trials in participants with type 1 diabetes.

Methods: Participants were eligible for an interview if they had exited one of the clinical trials within the previous 12 months. Participants were recruited by investigators at the clinical trial sites, and interviews were conducted by independent interviewers by telephone in accordance with a semistructured interview guide. Both interviewers and participants were blinded to treatment assignment. Qualitative analysis was conducted using ATLAS-ti version 7.5, and descriptive statistics were computed and summarized.

Findings: Across 3 countries, 41 participants were interviewed. Difficulty maintaining blood glucose within a desired range, described by participants as lack of blood glucose "stability," was the most concerning symptom that they reported, wanting to see it improved during the clinical trial because it negatively impacted their physical, mental, and emotional lives. Participants who reported symptom improvement also reported a positive psychosocial impact while taking the clinical trial medication. All participants who monitored ketones described themselves as being "pretty confident" to "very confident" that they could avoid diabetic ketoacidosis by monitoring both ketone levels and understanding the physical signs and symptoms of hyperglycemia.

Implications: Improvements in glucose stability and control were important to participants with type 1 diabetes, as these improvements were correlated with improvements in the participants' lives. ClinicalTrials.gov identifiers: NCT02384941; NCT02421510. (*Clin Ther*. 2019;41:2219−2230) © 2019 Published by Elsevier Inc.

Key words: exit interview, sotagliflozin, SGLT inhibitor, type 1 diabetes.

INTRODUCTION

The clinical importance of glycated hemoglobin A_{1c} levels in diabetes has been well documented[1−3]; however, little is understood about the impact of glycemic variability from the patient's perspective. In a recent conjoint analysis, the amount of time in the ideal glucose range of "most of the day" was the strongest driver of participants' choosing one therapy over another.[4] With the increased availability of continuous glucose monitoring allowing a detailed assessment of glucose fluctuations, clinicians and

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regulatory bodies are challenged to consider glycemic stability in addition to A_{1c} levels.

Two Phase III clinical trials of sotagliflozin (200 or 400 mg once daily) as an adjunct to insulin therapy for patients with type 1 diabetes (T1D) with inadequate glycemic control, inTandem1[5] and inTandem2[6] (hereafter referred to as clinical trials 309 and 310), were recently completed. The primary end point—efficacy at both dosages versus placebo—was met, as measured by statistically significant reductions in A_{1c} at week 24. Additional benefits of sotagliflozin over placebo included a greater time spent in the target glucose range, reduction in total insulin dose, and reduction in blood pressure. Participant-reported outcomes (PROs) data from clinical trials 309 and 310 showed increased treatment satisfaction, and reduced stress, as measured by the Diabetes Distress Screening Scale, among patients in the sotagliflozin arms compared with those in the placebo arms.[5,6]

To better understand the experiences associated with T1D and the importance of any changes experienced by patients during these studies, a qualitative interview study was conducted in a subset of patients who participated in trials 309 and 310.

PATIENTS AND METHODS
Study Design

Individual participant interviews were conducted in a subset of participants in clinical trials 309 (United States and Canada; ClinicalTrials.gov identifier: NCT02384941) and 310 (United Kingdom; ClinicalTrials.gov identifier: NCT02421510). Specifically, all eligible patients (regardless of treatment assignment, inclusion criteria below) from participating clinics were invited in a sequential, consecutive manner (by date of study exit) to participate in an interview. Each interview was conducted by telephone by a dedicated study-specific (309 or 310) interviewer and lasted ~60 min. Interviews followed a semi-structured interview guide designed to provide structure to the interviews by ensuring that data were collected in a systematic and consistent way and that interview objectives were met. The interview was composed of qualitative (open-ended, descriptive) questions and quantitative (closed ended) questions. These quantitative assessments were read aloud to each interview participant and answered during the interview.

All parties were blinded to treatment assignment at the time of the interview. Investigators were unblinded to data during the data analysis phase. All procedures and materials for this study were approved by RTI Health Solutions' institutional review board (IRB; United States), by Chesapeake IRB (Canada), and by HRA Ethics (United Kingdom). All interview participants provided verbal consent prior to the interview.

Inclusion Criteria

To be eligible for inclusion in this study, participants had to have completed, or have discontinued early from, clinical trial 309 or 310 at <12 months prior to interview scheduling, and be able to speak, read, and comprehend English. There were no exclusion criteria.

To facilitate participant recruitment, a comprehensive list of eligible participant numbers (IDs) per participating clinic was generated and provided to each of the participating clinical trial sites. To limit bias in sample selection, the participant lists included all participants, regardless of randomization assignment. Site staff contacted eligible participants on the list by telephone, starting with those who had most recently exited the study. Clinic staff then described the interview study to the participants using IRB-approved recruitment materials, and referred interested participants to the appropriate interviewer for the scheduling of an interview.

Interview Methods

Each interview was conducted according to a semistructured interview guide and was audio-recorded with participants' permission. The guide contained both qualitative (open-ended) questions to allow for spontaneous reporting, with targeted probes to ensure that specific research objectives were met, and quantitative (closed-ended) questions.

During the interviews, participants were asked to describe their pretrial experiences (symptoms and impacts) with T1D, their experiences during the clinical trial after randomization, as well as their satisfaction with T1D treatments. Participants were asked to report the T1D symptom that most concerned them, and the symptoms they most wanted to see treated with an effective T1D medication. Participants were questioned on their experiences

during the clinical trial and what changes, if any, they noticed during the trial. Participants who reported >1 treatment benefit were asked to identify the most important treatment benefit they experienced during the clinical trial, and to describe why that benefit was so important to them. All participants who reported any treatment benefit during the clinical trial were asked to discuss the potential impact(s) of those benefit(s). Participants were asked to rate their satisfaction with treatment before and during the clinical trial, on a 7-point scale ranging from 0 (very dissatisfied) to 6 (very satisfied). This scale was similar to the global satisfaction scale included in the Diabetes Treatment Satisfaction Questionnaire (DTSQ)[7] used for collecting PRO data during clinical trials 309 and 310.

Analysis Methods

A thematic analysis method was applied to analyze the interview field notes and transcripts.[8] Important concepts and dominant trends in each interview were identified and then compared across interviews to allow for the generation of themes or patterns in participants' responses. Participants' experiences and perceptions of change and treatment benefit over the study period were then described. The analysis was facilitated by coding software (ATLAS-ti version 7.5; Scientific Software Development, Berlin, Germany), and the initial coding framework was developed and adapted as the analysis progressed to incorporate emerging themes.

Additionally, descriptive statistics based on the quantitative data obtained during the interviews (eg, symptom improvements during the clinical trial) were computed and summarized (ATLAS-ti version 7.5).

RESULTS

From the 82 sites participating in the clinical trials, 9 US, 4 Canadian, and 7 UK sites participated in the qualitative interview study. Of the 1575 participants who were included in the clinical trials (trial 309, N = 793; trial 310, N = 782) 72 participants (4.6% of the total trial population) were eligible for the interview study (ie, had exited the clinical trial from 1 of the 9 clinical trial sites participating in the interview study, within the previous 12 months). Of these, 31 decided not to participate (reasons for nonparticipation were not collected). Interviews were scheduled with all 43 remaining participants, 41 of

which were completed, and 2 of which resulted in nonattendance by the interviewee.

The demographic and clinical characteristics of the study participants were similar to those of the overall populations of clinical trials 309 and 310 (Table I).

Background and Pretrial Experiences With T1D

All 41 participants reported difficulty maintaining their blood glucose within a desired range prior to the clinical trials. This difficulty was commonly described as frequent "high" (n = 40) or "low" (n = 32) blood glucose events (hyperglycemia or hypoglycemia, respectively). Thirty-seven participants reported higher-than-desired A_{1c} levels, and 35 participants also described a general lack of blood glucose stability, as demonstrated by the following sample quotes (participant number treatment assignment; P = placebo, Tx = sotagliflozin): "Too many lows, too many highs. Not enough time in the zone," (23_P); "[Blood glucose was] going high and wanting to fall asleep in my tracks, and then 2 h later starting to crash and starting to shake and sweat, and all those great things that go with it," (21_Tx); "My sugar would keep bouncing around no matter what I did. It would go high; it would go low. It was not stable," (03_Tx).

The most commonly reported "most concerning symptom" of diabetes before the trial was frequent high blood glucose events (n = 12), followed by higher-than-desired A_{1c} levels (often ascribed to blood glucose events by participants) (n = 10), hypoglycemia (n = 8), and overall lack of blood glucose stability (n = 6). When asked why particular symptoms caused the most concern, participants' responses often centered on both the short- and long-term negative health impacts that these symptoms had, or could have, on their lives, as demonstrated by the following sample quotes: "I guess the fear of the long-term consequences of frequent highs, specifically, like, on kidneys, eyes, feet, general health," (27_Tx); "I would have to say the fluctuation in sugar levels [are the most concerning] … [being] too high because basically if you're high, it's shortening your life, putting you at risk. … But on the same scale, a low is not healthy either because of … the shock that the body goes through with the adrenalin and the long-term effects of how it can affect your memory and everything," (25_P); "The one that concerns me the most is the A_{1c} levels

Table I. Demographic and clinical characteristics of the interviewed sample, eligible but did not participate sample, and overall sample from clinical trials 309 and 310.

Characteristic	Interviewed Sample (n = 41)	Interviewed and Eligible, Did Not Participate Sample (n = 31)	Overall Sample of Study 309 (N = 793)	Overall Sample of Study 310 (N = 782)
Male, no. (%)	24 (58.5)	14 (45.2)	383 (48.3)	406 (51.9)
Age, y				
Mean (range)	48.1 (26—70)	42.9 (22—68)	46.1 (18—79)	41.2 (18—78)
At diagnosis, mean (range)	23.7 (1—54)	21.1 (1—47)	21.7 (0—69)	22.8 (1—66)
Years since diagnosis, mean (range)	24.3 (4—60)	21.8 (1—48)	24.4 (1—64)	18.4 (1—59)
T1D treatment mode prior to study				
Insulin delivery, no. (%)				
Injection	19 (46.3)	20 (64.5)	320 (40.4)	581 (74.3)
Pump	22 (53.7)	11 (35.5)	473 (59.6)	201 (25.7)
Use of CGM prior to study	10 (24.4)	Not available	Not available	Not available
Treatment assignment, no. (%)				
Active treatment	27 (65.9)	22 (71.0)	525 (66.2)	524 (67.0)
200 mg	11 (40.7)	11 (50.0)	263 (50)	261 (49.8)
400 mg	16 (59.3)	11 (50.0)	262 (50)	263 (50.2)
Placebo	14 (34.1)	9 (29.0)	268 (33.8)	258 (33.0)
Participated in CGM substudy, no. (%)	4 (9.8)	3 (9.7)	136 (17.1)	142 (18.2)

CGM = continuous glucose monitor; T1D = type 1 diabetes.
The clinical trial demographic and clinical characteristics used to populate this table were provided to Research Triangle Institute Health Solutions (RTI-HS) by Lexicon.

simply because that's an indication of your average blood glucose level over time. And the higher your A_{1c}, the higher your blood glucose level and the greater the risk for other complications," (18_Tx).

Almost all participants (n = 39) reported that T1D had a negative impact on their life as seen in Table II. Participants commonly described these impacts as highly related. For example, the emotional impacts (eg, irritability or depression) associated with T1D symptoms often affected social and familial relationships; the physical impacts (eg, fatigue, shakiness) reduced participants' ability to accomplish tasks at home or at work, as exemplified by the following quote: "It [T1D] can make you depressed. It can make you angry. It can make you irritable. It can impact your ability to walk in a straight line. It's constantly, you're constantly thinking about what are you eating and how's that affecting your body chemistry. And how's exercising … is exercise impacting that. So let's just say that diabetes has a

pervasive effect on pretty much every aspect of your life," (18_Tx).

The most frequently reported impacts of T1D (with sample quotes) included:

Physical impacts (eg, how one feels physically, physical functioning, lower energy/increased fatigue) (n = 34): "When you have high blood sugars, you definitely feel more lethargic and lazy and do not want to do anything," (07_Tx); "I am just a little bit slower, a little bit more tired, get tired faster," (06_Tx).

Mood and emotional impacts (eg, depression, anxiety, sadness) (n = 31): "Like when your blood sugar is high, you are a little more angry sometimes, and you say get away from me; when it is low, you get so down about everything because you are just trying to get something to eat, and you feel basically horrible, so it is like from one rebound to the other, it is hard,"

Table II. Frequency of T1D impacts before the clinical trials. Data are given as the number (%) of patients.

Impact	Active Treatment (n = 27)	Placebo (n = 14)	All Patients (N = 41)
Physical (eg, how one feels physically, physical functioning, energy level/fatigue)	23 (85.2)	11 (78.6)	34 (82.9)
Mood/emotions (eg, depression, anxiety, sadness)	24 (88.9)	7 (50.0)	31 (75.6)
Daily activities in general (eg, exercise, self-care, travel, hobbies, driving)	19 (70.4)	8 (57.1)	27 (65.9)
"Quality of life" (mentioned specifically)	14 (51.9)	5 (35.7)	19 (46.3)
Self-esteem (eg, self-confidence, how one feels about themselves)	11 (40.7)	4 (28.6)	15 (36.6)
Daily activities at work (impact on any gainful activities [eg, absenteeism, productivity])	9 (33.3)	5 (35.7)	14 (34.1)
Social activities (eg, diminished desire or ability to participate in social activities such as going out with friends, family)	6 (22.2)	6 (42.9)	12 (29.3)
Family/family planning	6 (22.2)	3 (21.4)	9 (22.0)
Mental clarity (impact on ability to think clearly or quickly; fogginess)	3 (11.1)	4 (28.6)	7 (17.1)
Daily activities at home (impact on any non-gainful activities/ chores at home)	3 (11.1)	1 (7.1)	4 (9.8)

T1D = type 1 diabetes.

(14_Tx); "When I am having a lot of lows, I get really emotional and cry a lot and then I say things I do not mean. Then when I am having highs I am angry, I get mad, like we are kids. Just at the drop of a hat. That is mostly because your whole body just does not feel right," (08_P).

Activities of daily living (eg, exercise, self-care, travel, hobbies, driving) (n = 27): "I was really scared to be driving and it [blood glucose] drop on me. The highs, like I said, other than just being really tired, I was not so scared to drive with them. Lows, I would not drive. It would scare me. I would be driving, and it would happen so I would keep something in my car to cram [to eat]," (03_Tx); "It prevented me from doing certain things by limiting my energy and willingness to participate," (02_Tx).

Overall quality of life (n = 19): "It affects everything in my life I feel. It has affected my decision to have children, it affected how old I think I am going to live to be, my quality of life and my day to day, every day, everything I am doing. Everything kind of wears on you up to a certain point," (02_Tx);

"It [T1D] … it consumes my life. My whole life revolves around it," (08_P); "It's [T1D] life changing … It really is. It changes your life. Basically, if I don't inject the insulin, I die," (39_P).

Full participants' descriptions of the impact of T1D in different domains are shown in Supplemental Table I (see online version at https://doi.org/10.1016/j.clinthera.2019.09.003).

Treatment Desires

When asked what specific symptom participants most wanted to see treated/improved in the clinical trial, lack of stable blood glucose was most commonly reported (n = 16), followed by higher-than-desired A_{1c} (n = 15), and frequent hyperglycemic events (n = 7) (Table III). When asked why improvement in these symptoms was so desired, responses included that these improvements could reduce the risk for long-term consequences, improve quality of life, and make them feel in control of their blood glucose: "If I get my blood sugar under control and I have my weight down, then I'll be happy.

Table III. Frequency of symptoms that participants most wanted to see treated in clinical trials. Data are given as the number (%) of patients.

Symptom Most Important to Improve	Active Treatment (n = 25)	Placebo (n = 12)	All Patients (n = 37)
Lack of stable blood glucose	10 (40.0)	6 (50.0)	16 (43.2)
Higher than desired A_{1c}	9 (36.0)	6 (50.0)	15 (40.5)
Weight gain	2 (8.0)	4 (33.3)	6 (16.2)
Frequent hypoglycemic events	0	4 (33.3)	3 (8.1)
Increased use of insulin over time/less effective insulin	3 (12.0)	2 (16.7)	5 (13.5)
Frequent hyperglycemic events	6 (24.0)	1 (8.3)	7 (18.9)
General health	1 (4.0)	0	1 (2.7)

[Better glucose control means] what I'd like to see is have my sugars more often in the target range," (38_Tx); "[Glucose instability] affects my life more than anything to go from being really high to being really low and then a lot of the time go really high again. It just affects the way I feel," (12_Tx); "[Hyperglycemia] Probably those occasional highs. Why was that really what you wanted to see improve? Just to get rid of that lethargic tired feeling," (16_Tx).

Experiences During the Clinical Trials

The frequencies of reported symptom improvement over the course of the clinical trials are shown in Table IV, and selected participants' descriptions of improvements in their symptoms are shown in Supplemental Table II (see online version at https://doi.org/10.1016/j.clinthera.2019.09.003). Of the 41 participants, 33 (80.5%; 26 on sotagliflozin, 7 placebo) reported improvements in at least 1 symptom. The most frequently reported improvements included fewer hyperglycemic events (n = 31), increased blood glucose stability (n = 30), more effective/reduced insulin use (n = 28), lower A_{1c} (n = 28), and fewer hypoglycemic events (n = 17) (see Table IV).

When asked to rate the importance of improvements on a scale of 1−5 (Figure), greater blood glucose stability (mean, 4.7) and reductions in A_{1c} levels (mean, 4.6) were rated as the most important improvements, closely followed by (and described as highly related to) reductions in "high" (mean, 4.5) and "low" (mean, 4.4) blood glucose events.

More than half of the participants noted that 3 specific improvements experienced during the clinical

trial were "very" or "extremely" important (Figure): fewer hyperglycemic events, greater blood glucose stability, and reduced A_{1c} levels. When asked to describe why these improvements were so important, a typical participants' response was: "I guess the insulin going down would be the most important, with the blood sugar levels being more stable." Why are those 2 really the most important? "Well, it affects your whole body, it affects your weight, it affects you mentally, just everything. Once you get those going down … if you maintain that high, you lose focus, you start losing everything, you start gaining weight. The most important thing is getting that blood sugar level [stabilized]," (06_Tx).

All but 1 (97%) of the interview participants who reported symptom improvement also reported that these improvements had a positive impact on their lives. These positive impacts included improvements in mood/emotions (n = 23), physical functioning (n = 16), self-esteem (n = 11), overall quality of life (n = 9), and a greater ability to accomplish activities (both in general [n = 6], and at work/home [n = 6]). Participants typically described these positive impacts as follows: "I felt better about myself. About how the study was going. It made me feel good that all these things were happening. You always have that thought … I have these high blood sugars, and I have this low blood sugar, and it is like a complete 180 when I was on it [study medication]. Consistently better so you do not have to worry as much," (07_Tx); "Yes, my sugars went down … Then of course with my sugars going down my A_{1c} went back into a better range. Other than not having highs and high symptoms, I just felt better … I was not tired as much. I actually started walking again too

Table IV. Frequency of reported symptom improvement over the course of the clinical trials. Data are given as the number (%) of patients.

Symptom Improvement	Active Treatment (n = 27)	Placebo (n = 14)	Total (N = 41)
Fewer hyperglycemic events	24 (88.9)	7 (50.0)	31 (75.6)
Active treatment			24 (58.5)
Placebo			7 (17.1)
Increased blood glucose stability	24 (88.9)	6 (42.9)	30 (73.2)
Active treatment			24 (58.5)
Placebo			6 (14.6)
Reduced insulin/improved	21 (77.8)	7 (50.0)	28 (68.3)
Active treatment			21 (51.2)
Placebo			7 (17.1)
Lower A1C	23 (85.2)	5 (35.7)	28 (68.3)
Active treatment			23 (56.1)
Placebo			5 (12.2)
Fewer hypoglycemic events	14 (51.9)	3 (21.4)	17 (41.5)
Active treatment			14 (34.1)
Placebo			3 (7.3)
Weight loss	14 (51.9)	2 (14.3)	16 (39.0)
Active treatment			14 (34.1)
Placebo			2 (4.9)
Lower blood pressure	3 (11.1)	0 (0)	3 (7.3)
Active treatment			3 (7.3)
Placebo			0 (0)
Reduced neuropathy	1 (3.7)	1 (7.1)	2 (4.9)
Active treatment			1 (2.4)
Placebo			1 (2.4)
Less extreme highs and lows in blood glucose	3 (11.1)	1 (7.1)	4 (9.8)
Active treatment			3 (7.3)
Placebo			1 (2.4)

when my daughter was at dance and things like that," (08_P).

In general, participants who saw a reduction in the number of hypoglycemic events also reported feeling more confident about not having them.

Of the 41 interviewees, 2 described experiencing diabetic ketoacidosis (DKA) during the clinical trial. When probed about ketone monitoring and fear of DKA, about half of the participants (n = 20; 48.8%) reported undergoing at least occasional monitoring both before and during the clinical trial. Participants reported experience with both urine and/or blood test strips, and most commonly described the process as easy to do. All participants who monitored ketones reported some level of confidence that they could avoid DKA by monitoring both ketone levels and understanding the physical signs and symptoms of hyperglycemia.

Treatment Satisfaction

During the interview process, participants from the active treatment group (n = 27) rated their satisfaction as higher than before the trial (5.5 vs 3.9, see Table V). Participants from the placebo group (n = 14) rated their satisfaction during the trial as lower than before the trial (3.7 vs 4.3). Participants'
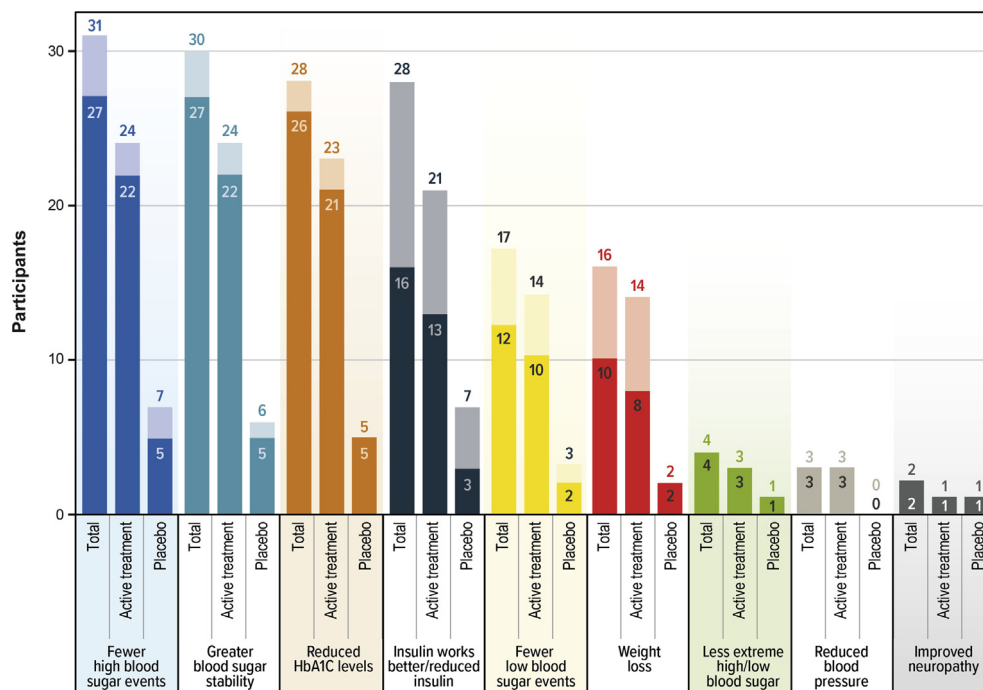
Figure. Frequency of reported T1D symptom improvements and importance ratings (N = 41). Importance rating scale: 1 = not at all important; 2 = a little important; 3 = moderately important; 4 = very important; 5 = extremely important. The numbers above each bar indicates the total number of participants who reported a specific symptom improvement. The numbers in the darker shaded area of each bar indicate the number of participants who reported their improvement as "very" or "extremely" important. Hb = hemoglobin; T1D = type 1 diabetes.

Table V. Interview and clinical trial treatment satisfaction scores* before and during the clinical trials. Data are given as mean (range).

Treatment Group	Interview Questions: Satisfaction		Clinical Trial Questions: DTSQ Item 1	
	Before	During	Baseline	Week 24
Active treatment (n = 27)	3.9 (0–6)	5.5 (3–6)	4.2 (1–6)	5.1 (0–6)
Placebo (n = 14)	4.3 (3–5)	3.7 (0–6)	4.1 (3–5)	3.8 (0–6)
All patients (N = 41)	4.0 (0–6)	4.9 (0–6)	4.2 (1–6)	4.7 (0–6)

* Participants were asked to rate their satisfaction with treatment before and during the clinical trial, on a 7-point scale ranging from 0 (very dissatisfied) to 6 (very satisfied).

reasons for increased satisfaction during the trial were directly related to the symptom improvements that they experienced and the positive impact those improvements had on their overall well-being, as exemplified by the following answers to the question, "What specifically influenced your response to say that it was a [6]—that you were very satisfied?": "Everything. The weight loss, the consistency in my

blood sugars, everything. It was amazing. The part that really sucked about it was when it was over," (07_Tx); "Because my whole outlook and the way I felt, felt so much better. You feel that you have a better quality of life. You can participate. … You lost weight, your sugars went down, you felt so much better. I really, really loved it," (06_Tx).

Similarly, a higher proportion of patients on active treatment (88.9%) than placebo (42.9%) stated that they would have continued study medication (Table VI).

Adverse Events

Although not specifically probed during the interviews, a total of 19 potential adverse events were recalled by 12 participants. Of these, all but 1 (gas) had previously been reported during the clinical trial. No new tolerability signals were identified.

DISCUSSION

This study is one of the first to capture participants' own voices describing the general burden of T1D in their lives, their hopes for a new therapy before initiating it, and their subjective experiences and descriptions of symptom changes while on therapy. These qualitative data provide a valuable supplement to the efficacy and tolerability data derived from the clinical trials themselves,[5,6] giving insights into the trial participants' own perceptions of the benefits of a dual sodium−glucose cotransporter 1 and 2 inhibitor as a therapy to adjunct insulin, which may not be captured sufficiently by conventional clinical and participant-reported end points. Asking "why" participants expressed their opinions and choices, in addition to "what" they feel they achieved during the clinical trial, enriches our understanding of the participants' experience. An important development in PRO studies, as regulatory bodies, payers, and health care professionals are becoming increasingly interested in determining the participants' perspective on the overall risk−benefit profile of a drug.[9]

This study yielded a number of important insights in addition to the findings of the clinical trials. Participants consistently reported the value of glucose stability and control, which is in accordance with findings from previous literature on the importance of glycemic stability to participants with T1D.[10,11] Glycemic fluctuations are seen as postprandial glycemic spikes and minor hypoglycemia. A study analyzing data across the United Kingdom, the United States, and Germany found that 61.5% of the study population had experienced postprandial hyperglycemia in the previous week.[12] Glycemic variability is known to be associated with mood changes, anxiety, and absenteeism (inability to work).[13,14]

The findings from this study add a new dimension to the body of evidence by allowing participants to discuss this in an unprompted manner, using their own words. Interpretation of quantitative PRO measures or those reliant on Likert scales (always/sometimes/often/never) may be affected by participant habituation effects—in which participants grow accustomed to their condition and so rate the effects as less severe. By recording detailed descriptions of life experience with T1D, we were able to record a clearer picture of the effects of treatment on participants' well-being.

The majority of the participants who described improved glycemic control during the trial clearly articulated that the change was meaningful and had a positive impact on their lives. These positive impacts spanned several domains of well-being, including mood/emotions, physical functioning, self-esteem, and improvements in overall quality of life. The positive impacts on the lives of patients provide important insights into the relevance of end points, including time in range and patient reported outcomes. These

Table VI. Participants' desire to continue study medication after the trials. Data are given as the number (%) of patients.

Would have continued study medication?	Active Treatment (n = 27)	Placebo (n = 14)	All Patients (N = 41)
Yes	24 (88.9)	6 (42.9)	30 (73.2)
No	2 (7.4)	8 (57.1)	10 (24.4)
Unsure	1 (3.7)	0	1 (2.4)

end points can support informed discussions and participant-support initiatives.

People reported their satisfaction from clinical trials 309 and 310 during the interviews at levels similar to those from the DTSQ at the time that the trial was being conducted. This finding suggests that their quantitative perception recall of treatment was valid. In participants on active treatment, increases in satisfaction from before the trial to during the trial, on both the survey during the interview and on the DTSQ, related to the symptom improvements that they experienced and the positive impact that those improvements had on their overall well-being. The improvement in well-being has potentially important implications for adherence and persistence. These results suggest that sotagliflozin provides an important treatment benefit in participants due to its ability to improve glycemic control.

Gaining a deeper insight into the participant perspective helps us to understand the variables associated with participants' personalized decision-making processes, particularly their perceptions of the benefits and risks of therapy that manifest in their overall satisfaction that was captured within the trial and during the exit interviews. When questioned about the risks of DKA, the study results suggest that participants understood the risks involved, and did not find ketone monitoring to be burdensome, but regarded it as an acceptable procedure given the benefits of therapy.

Strengths and Limitations

The strengths of this study included recruiting all eligible participants regardless of their treatment status or completion of the 52-week trial, and keeping both participants and interviewers blinded to treatment assignment during the interview. Prior experience interviewing subjects in clinical trials has shown that clinically meaningful experiences can be captured with as few as 20 participants.[15] This precedent was a consideration when determining the sample size of this study.

There is potential for selection bias in interview studies; however, similarities in baseline characteristics and proportion of placebo participants between interview participants and the overall clinical trial provided reassurance that selection bias may have been minimal. Additionally, although 41 participants is a small percentage of the total trial

population, this is not unusual for exit interviews. Mean DTSQ scores at the end of the interview study and clinical trial also appeared to be similar, reflecting the proper selection of participants without regard to participant response.

To examine the potential for recall bias, satisfaction scores from interviews were compared to those obtained during the trial. The context of presenting these questions was different for the 2 settings, the items themselves were slightly different, and differences in results do not necessarily suggest a lack of recall. Nonetheless, some relevant findings were evident. The mean baseline satisfaction scores on the DTSQ, reported in the context of the clinical trial, were slightly higher than what was recalled for pretrial experiences during the interview, but there was still a relatively strong correlation between the 2 ratings (0.62). There was a very strong correlation (0.90) between DTSQ scores at the end of the trial (week 24) and interview reports of satisfaction during the trial. There are several possible explanations for the similarities in clinical trial and interview ratings of satisfaction. It is possible that participation in the interviews occurred soon enough after study completion for participants to accurately recall their experiences. Additionally, it is possible that satisfaction reports were similar because the benefits were meaningful (and therefore not forgotten), or because the loss of benefits in the months after study completion reinforced the memory of the clinical trial. The close similarities between these interview results and DTSQ scores at the end of the clinical trial suggest that participants were able to recall their clinical trial experiences accurately.

CONCLUSIONS

In this interview-based study, participants with T1D reported that improvements in glycemic stability and control were the most meaningful to them due to improvements to their physical functioning, self-esteem, and overall quality of life.

acquired the data. All of the authors interpreted the data and made critical revisions to the manuscript. All of the authors have approved the final article.

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APPENDIX A. SUPPLEMENTARY DATA

The following are the Supplementary data to this article:

APPENDIX A. BURDEN OF T1D AND PARTICIPANTS' DESCRIPTIONS OF IMPACTS PRIOR TO STARTING CLINICAL TRIALS 309 AND 310

Impact(s)	Placebo (n = 14) n (%)	Treatment (n = 27) n (%)	Total (N = 41) n (%)	Quote
Physical (e.g. how one feels physically, physical functioning, energy level/ fatigue)	11 (78.6)	23 (85.2)	34 (82.9)	Walking, exercising. It is hard because [inaudible] exercising is really difficult. (11_Tx) Because you get sweaty and the shakes and you know your blood sugar is getting low, but the longer you have it, those symptoms do not appear right away. (07_Tx) When you have high blood sugars, you definitely feel more lethargic and lazy and do not want to do anything. (07_Tx) I am just a little bit slower, a little bit more tired, get tired faster as you get older, I guess that comes with it. (06_Tx) Dry skin first, headaches, when my sugar is low I get shaky and feel really bad. (12_Tx) I get really tired, really bad headaches, just do not want to move, do not want to do anything. If it is extremely high, then I get sick to my stomach. (03_Tx) Physically I noticed I was very tired. I was needing sleep. I always wanted to sleep. I looked forward to Saturdays so I could sleep till 9 or 10:00. I just, I was just sleepy. And I'd go to bed and just hit the pillow and I'd be out. (15_Tx) For a low sugar hypoglycemic episode, I would become very sweaty, agitated, sometimes nauseous or have headaches, become obsessed with food and eating. I would try to eat something quickly so that I felt better… With the highs, dry cotton mouth, headache, sometimes nauseous if they were very high, lethargic. (10_P) When your sugar is always high, you are a lot more tired, grouchy, you urinate more, thirsty. (08_P)
Mood/emotions (e.g. depression, anxiety, sadness)	7 (50.0)	24 (88.9)	31 (75.6)	Just the hassle of constantly checking, worrying if it is too high, too low… Yes. Worrying I am going to pass out and die from the lows. I had a friend that happened to. Am I going to do it if my grandchildren are here? That scares me. (03_Tx) Higher stress and some depression. (02_Tx) It does affect them; it is like when your blood sugar is high, you are a little more angry sometimes, and you say get away from me; when it is low, you get so down about

Impact(s)	Placebo (n = 14) n (%)	Treatment (n = 27) n (%)	Total (N = 41) n (%)	Quote
				everything because you are just trying to get something to eat, and you feel basically horrible, so it is like from one rebound to the other, it is hard. (14_Tx)
				It has been very hard because there are times when I am very emotional. When I am having a lot of lows, I get really emotional and cry a lot and then I say things I do not mean. Then when I am having highs I am angry, I get mad, like we are kids. Just at the drop of a hat. That is mostly because your whole body just does not feel right and then somebody is doing something that is making you mad and I just... not snap, but I have a trigger. I get mad easier. (08_P)
				I'm a dad with 2 kids who are now teenagers. So it's the emotional impact of having them watch me go through this and my spouse. The lack of being able to be the father at times that I want to be. And to hear that this being a genetic disease, they are predisposed to following my path, which is not something I want. We waited 8 years to have kids because I had to get over the mental hurdle of 'what if.' (23_P)
				Even if it's just going to the beach for the day with the dog. You've got to think about when you eat, when you inject, how long are you going to be out... It does make a difference. (39_P)
				I think the thing is that it affects my life 24/7. It's a constant thought, pretty much. There won't be an hour in the day, or a half hour in the day, that I don't think about my diabetes. If I go out for a walk, I have to be aware that I'm likely to go hypo, and that is the case. (40_Tx)
Daily activities in general (e.g. exercise, self-care, travel, hobbies, driving)	8 (57.1)	19 (70.4)	27 (65.9)	*I was really scared to be driving and it drop on me. The highs, like I said, other than just being really tired, I was not so scared to drive with them. Lows I would not drive. It would scare me. I would be driving, and it would happen so I would keep something in my car to cram [to eat]. (03_Tx)*
				It prevented me from doing certain things by limiting my energy and willingness to participate. (02_Tx)
				I am very routine. It is very hard for me to get out of a routine. I eat dinner at the same time, I eat lunch at the same time. So, when you work, I am a normal adult, working. It is just in my life, it consumes my life. My whole life revolves around it. (08_P)

. (*Continued*)

Impact(s)	Placebo (n = 14) n (%)	Treatment (n = 27) n (%)	Total (N = 41) n (%)	Quote
				And I hate that [T1D] is the first thought that comes in my mind before I want to go out, before I want to go to the gym, before I want to do something with my kids, before I travel, before anything. It's the check, it's the how are you, it's the fear that something happens while you're then trying to go about your day and trying to be prepared for it and manage it to the best of your abilities. But knowing that you can't always succeed. (23_P)
Quality of life	5 (35.7)	14 (51.9)	19 (46.3)	It affects everything in my life I feel. It has affected my decision to have children, it affected how old I think I am going to live to be, my quality of life and my day to day, every day, everything I am doing. Everything kind of wears on you up to a certain point. (02_Tx)
				It is a mix of things, it is everything from, is this [T1D] going to kill me in the next 10 years? How am I going to continue to get medicine? Did I not get that job because I am diabetic? Did I not do this thing? Yes, it affects everything. Does it bum people out? Does this keep people at a distance? (05_P)
				I mean would it be different if I didn't have to think about it? Would it be easier if I didn't have diabetes? Absolutely. But quality, I think I have a pretty good quality of life. But would it be easier? Yeah. I mean like even something as simple as traveling and having the extra stuff to take or trying to get on the plane with syringes and vials of insulin and doctor's notes and all that medication. Yeah, it is tricky. (29_P)
Self-esteem (e.g. self-confidence, how one feels about themselves)	4 (28.6)	11 (40.7)	15 (36.6)	I would say the lack of education of others is actually very impactful on your self-esteem and your mental state and how you feel about yourself. (35_Tx)
				I am a perfectionist, and in school I always had to be the straight-A student, and diabetes feels like I have been given a test and I am failing. (12_Tx)
				I think I am very hard on myself when it comes to that. I do not think I say it, but I feel it inside. I do not really voice it, but I know I am disappointed in myself a lot because of it. Then of course, my weight too. I would love to be back like I was in my 20s but that is not going to happen. (08_P)
				Sadly, it probably defines you. It defines me first and foremost and again, I hate that. But everything I do has to be done with that in the back of your mind first. (23_P)

Impact(s)	Placebo (n = 14) n (%)	Treatment (n = 27) n (%)	Total (N = 41) n (%)	Quote
Daily activities at work (impact on any gainful activities e.g. absenteeism, productivity.)	5 (35.7)	9 (33.3)	14 (34.1)	*Yes, I would say the shaky feeling. The unsteady feeling impacts my work life. (12_Tx)* *And there have been times when if I'm at work and my blood sugar drops, and if I'm dealing with somebody or I'm in a meeting or something's happening and my blood sugar drops, I feel ... the only way I describe it as it like cotton brain. Where everything's kind of clouded, and it's hard to piece words together and sentences together properly. (29_P)* *I don't work right now. I am on long-term disability [because of T1D]. (25_P)*
Social activities (e.g. diminished desire or ability to participate in social activities such as going out with friends, family)	6 (42.9)	6 (22.2)	12 (29.3)	*Oh, I was really down and depressed and you couldn't do this and a lot of things we used to do and eat and I felt like an outsider. And especially, I was working ... And they would have like lunches or like they had Marble Slab ice cream one day come into the school and you could have your own sundae and all this. And I didn't get to partake because I have diabetes. I always felt left out. I mean just stuff like that where I felt left out and not included, so. (15_Tx)* *Just that everything you do is harder. I never discuss it with anybody, so no one really knows because I do not bring it up in conversation. Obviously in your inner circle. Just remember one thing in life, people do not want to know what is wrong with you, they want to know what is right with you. So, you find a way to try to deal with it and keep it to yourself. (13_Tx)* *I would like to drink more. I would like to be able to order an adult cocktail and not have to worry about what it is going to do, how much insulin do I take? I would like to just have a normal adult life. (08_P)* *You cannot just go out and go to dinner with your friends and just have the filet mignon and a side of potatoes; you have got to think, well I will have the filet mignon, but maybe I should have vegetables instead of the potatoes. Or everybody is going to sit down with pie and coffee and you are sitting there maybe with a plain piece of cake if you can get away with it [inaudible] you do not have pie, you just have coffee. So, it is always something that singles you out sometimes. (04_P)*

. (*Continued*)

Impact(s)	Placebo (n = 14) n (%)	Treatment (n = 27) n (%)	Total (N = 41) n (%)	Quote
Family/family planning	3 (21.4)	6 (22.2)	9 (22.0)	*Probably the snippiness with my family affects me the most just because it puts a strain on the relationship with my wife. That would probably be the biggest. (7_Tx)* *It has affected my decision to have children (02_Tx)*
Mental clarity due to low or high blood glucose	4 (28.6)	3 (11.1)	7 (17.1)	*You get kind of snippy with people, or you forget to do things. It is just that you do not feel right. (07_Tx)* *Yes, the mental fogginess, the whole body feeling draggy, you just have no energy, the muscles ache. Everything. That is the best way. (12_Tx)* *It is difficult to think, difficult to speak. (05_P)* *I was just sitting around, but I get kind of blank (01_P)*
Daily activities at home (e.g. impact on any non-gainful activities/chores at home)	1 (7.1)	3 (11.1)	4 (9.8)	*Like I said, except for during a high. I would not have any energy and there were plenty of things I wanted to do or needed to do. Especially at home, I just could not do them … painting, or even sweeping and mopping. Just no energy to do it. (06_Tx)* *I make sure that I am not exerting myself too much because I would have to stop every hour or hour and a half and go get something to eat. Even at home when I am doing chores around the house, if I start sweating and within the hour my blood sugar is low, I have to go and eat something. (07_Tx)*

APPENDIX B. SELECTED PARTICIPANTS' DESCRIPTIONS OF IMPROVEMENT IN T1D SYMPTOMS DURING THE CLINICAL TRIALS

Improvement	Quotes
Fewer hyperglycemic events	*My blood sugar was lowered. (02_Tx)* *Yes, my sugars went down. Which was what the pill was supposed to do. (08_P)* *I really felt like it was cutting down the spikes that I might have. (33_Tx)*
Increased blood glucose stability	*Because that level stayed level instead of going up and down. There was more of a level there. (06_Tx)* *My sugars were more stable. I had fewer spikes. (12_Tx)* *It did seem like I was in the good zone more often. (25_P)* *I got longer periods [of stability] and more stable. (32_Tx)* *I had more normal range blood sugars, which is just great. (40_Tx)*

Improvement	Quotes
Decreased insulin use/more effective insulin	*[I] was probably taking 60 units a day, and that dropped to 40. So that was the first thing that I really saw, the insulin dosages going down. (06_Tx)*
	They started lowering my insulin dose I was taking. (03_Tx)
Lower A1C	*I had my absolute best A1C ever while doing that study. (31_Tx)*
	I started the program, it was 9, it changed, and then really at the conclusion of [the trial], it was 7. (13_Tx)
	My A1C came down to the levels that we wanted it to be at. (12_Tx)
Fewer hypoglycemic events	*I think I had less lows when I was on the study. (15_Tx)*
	I think I had fewer incidents of low blood sugar as well. (33_Tx)
Weight loss	*But while on the trial, I did notice that I lost weight even if I was eating the same amount of food or eating healthy, I just lost more weight, a significant amount while on the trial. (19_P)*
	I think I lost about 7 pounds. (11_Tx)
	I was 275 when I started the study, and at the end of the year, I weighed around 250. (07_Tx)
Lowered blood pressure	*It seemed to get lower and a little bit more consistent as the trial went on. (33_Tx)*
	My blood pressure went down. (37_Tx)
Less extreme high and low blood glucose	*When the highs occurred, they were not as high. (16_Tx)*
	I would just say that the overall, the highs weren't quite as out of control. Like, sometimes when you get a high, it's just, like, off the wall high, like you're looking at 22 type of thing. And it just seemed like things were just a little tighter. Like, if I had a high, it wasn't crazy high. (25_P)
	The peaks and valleys certainly reduced the frequency and they weren't as extreme. (21_Tx)